Original paper

Non-alcoholic fatty liver disease in Poland: how and at what stage is diagnosed, and how is treated. A survey study

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Abstract

Introduction: Epidemiological studies show an increasing incidence of overweight and obesity all over the world, leading to an increase in the number of patients consulted due to liver damage.

Aim: Assesement to which doctors (general practitioners or specialist) refer patients with elevated liver enzymes in Poland, how they are diagnosed and treated.

Material and methods: We conducted questionnaire surveys among 1322 doctors of various specialties to find the most common causes of liver disease, at which stage of the disease patients reported to doctors, and what schemes of management are followed.

Results: Non-alcoholic fatty liver disease (NAFLD) was the most common cause of abnormal liver enzymes (59.7%). Patients with liver damage most often reported to internal medicine specialists (59%) and gastroenterologists (27.5%). The diagnosis was based on abnormal aminotransferases (80.8%) and abdominal ultrasound examination (89.9%). Computed tomography/magnetic resonance imaging (50.2%) and liver biopsy (22.4%) were used to assess fibrosis. Almost all respondents recommended reduction of body mass and lifestyle changes, and less than half (46.4%) recommended pharmacological treatment.

Conclusions: NAFLD was the most common liver disease that was the reason for medical consultations, but its incidence seems to be underestimated due to referral for further diagnostics only in patients with abnormal aminotransferases. The diagnostic methods used to assess the severity of the liver fibrosis and the recommended pharmacological treatment varied depending on the physician's specialisation and the centre's reference level.

Introduction

The results of studies indicate a worldwide increasing incidence of non-alcoholic fatty liver disease (NAFLD), with the highest prevalence exceeding 25% in the Middle East and South America, and the lowest in Africa [1]. Most often, NAFLD is associated with obesity, diabetes type 2, and metabolic syndrome [1, 2], but also affects about 7% of lean people [3]. Cohort studies in a large group of patients revealed that NAFLD can develop in overweight and obese people without metabolic disorders, which may suggest that the obesity itself increase the risk of NAFLD [4]. NAFLD is twice as frequent in men as in women [5]. NAFLD is an important factor in the development of liver cirrhosis and hepatocellular carcinoma (HCC) – indications for liver transplantation [6].

Liver biopsy is the only method that enables the differentiation of non-alcoholic fatty liver (NAFL) from non-alcoholic steatohepatitis (NASH), because neither clinical evaluation nor biochemical tests allow unequivocal exclusion of NASH, which may result in progressive fibrosis, cirrhosis, or HCC [7].

Significant obesity increases the risk of NASH and intensity of fibrosis from 10% to 30% [8].

American prognosis estimates an increase in the overall prevalence of NAFLD by 2030 to 33.5%, an increase in the number patients with NASH from 20% to 27%, an increase of 168% in the number of patients with end-stage liver cirrhosis, an increase of 137% in the number of patients with NAFLD-derived HCC, and a 178% increase in the number of hepatic-related deaths [9].

We decided to perform this study to check which doctors (general practitioners or specialist) patients with elevated liver enzymes are referred to in Poland, and how they are diagnosed and treated.

Aim

We wanted to assess what, in the opinion of doctors, is the most common cause of liver damage and at what stage of the disease patients report to the doctor, how they are diagnosed and treated in Poland, and whether it is related to the doctors' specialisation and place of work.

Material and methods

In cooperation with the Chair of Epidemiology and Preventive Medicine of the Jagiellonian University, we prepared a questionnaire containing 12 questions (some of them with multiple answers). The approval of the Bioethical Committee of the Jagiellonian University was obtained to carry out the study.

Questionnaires were collected by interviewers from the doctors who agreed to participate.

The questionnaire survey involved 1322 physicians, specialists in family medicine, internal medicine, gastroenterology, infectious diseases, cardiology, and diabetology working in primary health care, specialistic outpatient clinics, hospitals and clinical wards, and diagnostic laboratories. The average age of the respondents was almost 34 years (mean age 33.926 years).

Statistical analysis

The statistical analysis of the obtained responses was made using the IBM SPSS Statistics 25 package. In order to check if there were statistically significant differences between two independent groups, the Mann-Whitney *U* test was used.

Analysis using the χ^2 test allowed us to check whether the compared groups were the same size, as well as whether there was a statistically significant relationship between the nominal variables (γ^2). The *p*-value < 0.05 was considered statistically significant.

Table I. Therapeutic recommendations received by patients with NAFLD

Recommendations for patients diagnosed with NAFLD	*N*	%
Body mass reduction	1236	93.5
Increased physical activity	1101	83.3
Introduction of a low-fat diet	1091	82.5
No recommendations	12	0.9

Results

Among the respondents, the largest group comprised specialists in internal medicine (*n* = 780, 59%) and gastroenterologists (*n* = 363, 27.5%) working in hospital wards (*n* = 780, 59%) and specialist outpatient clinics (*n* = 418, 31.6%).

Significantly more physicians wrote that the most frequent cause of abnormal liver enzymes among patients reporting to them was NAFLD, $\gamma^2(1) = 49.57$, $p < 0.001$ and alcoholic liver disease, $\gamma^2 (1) = 38.63$, $p < 0.001$.

Analysis using the *U* Mann-Whitney test showed that the average age of doctors who consulted weekly 1–5 patients with NAFLD was statistically significantly lower (mean ± SD: 43.98 ±11.97) compared to doctors who consulted larger number of patients (47.16 ±25.17), $p < 0.05$.

Significantly more respondents concluded that NAFLD affects patients aged from 31 to 50 years (57.5%, $\gamma^2(1) = 29.65$, $p < 0.001$) and from 51 to 70 years (42.1%).

The respondents gave ambiguous answers concerning who is more often affected by fatty liver: 44.8% of respondents stated that in their opinion liver steatosis affects mainly men, and 41.1% reported that it is equally common in men and women.

The majority of the surveyed doctors stated that among patients diagnosed by them NAFLD was most often accompanied by: obesity, $\gamma^2(1) = 936.78$, $p < 0.001$; lipid disorders, $\gamma^2(1) = 476.88$, $p < 0.001$; and type 2 diabetes, $\gamma^2(1) = 345.67$, $p < 0.001$ (Table I). Over three-quarters of respondents stated that patients with NAFLD most often refer to the doctor at the stage of non-alcoholic fatty liver (NAFL), $\gamma^2(1) = 392.13$, $p < 0.001$.

Respondents stated that they mainly based NAFLD diagnoses in their patients on: abdominal ultrasound examination, $\gamma^2(1) = 842.56$, $p < 0.001$; liver enzymes activity analyses, $\gamma^2(1) = 501.21$, $p < 0.001$; or anamnesis and physical examination, $\gamma^2(1) = 29.65$, $p < 0.001$. In the diagnostics of fibrosis advancement, respondents primarily recommended imaging examinations: computed tomography (CT) and magnetic resonance imaging (MRI) as well as liver biopsy, and far less frequently FibroScan and elastography (Table II).

The χ^2 analysis did not reveal any statistically significant relationships between the specialty or the

workplace of respondents and the type of procedures ordered to diagnose or evaluate the advancement of liver damage in patients with NAFLD.

Non-invasive tests (SteatoTest, NashTest, FibroTest, cytokeratin 18 concentration) are ordered primarily by infectious disease specialists and diabetologists, $\gamma^2(5) = 45.02$, $p < 0.001$. Liver biopsy is ordered primarily by infectious diseases specialists, $\gamma^2(5) = 37.52$, $p < 0.001$.

Analysis of the type of diagnostic tests recommended to assess fibrosis depending on the physician's specialisation and workplace showed that: FibroTest is ordered primarily by gastroenterologists and infectious disease specialists, $\gamma^2(5) = 12.06$, $p < 0.05$, working in a specialist outpatients clinic, $\gamma^2(4) = 13.95$, $p < 0.01$. Similarly, FibroScan, $\gamma^2(5) = 147.02$, $p < 0.05$ is ordered primarily by doctors with a specialisation in infectious diseases and gastroenterology working in a specialist outpatient clinic, $\gamma^2(4) = 54.32$, $p < 0.001$. In contrast, elastography is ordered by gastroenterologists and infectious disease specialists, $\gamma^2(5) = 78.84$, $p < 0.001$, working in a clinical ward; $\gamma^2(4) = 32.84$, $p < 0.01$.

CT/ MR is ordered by cardiologists, diabetologists, and specialists in internal medicine, $\gamma^2(5) = 18.79$, $p < 0.01$, working in a clinical ward and diagnostic laboratory, $\gamma^2(4) = 15.41$, $p < 0.01$.

Liver biopsy in patients with NAFLD for the diagnosis of the disease, assessment of fibrosis stage, and exclusion of other causes of liver damage was ordered primarily by specialists in infectious diseases and gastroenterology, $\gamma^2(5) = 56.92$, $p < 0.05$, working in a clinical ward or specialistic outpatient clinic, $\gamma^2(4) = 31.27$, $p < 0.001$.

Regarding in the treatment, the majority of the surveyed doctors recommended the following to their patients with NAFLD: weight reduction, $\gamma^2(1) = 1000.38$, $p < 0.001$; increase in physical activity, $\gamma^2(1) = 585.78$, $p < 0.001$; and introduction of a low-fat diet without simple sugars, $\gamma^2(1) = 559.45$, $p < 0.001$ (Table I).

Among the various forms of pharmacological treatment, fewer than half of the respondents indicated the following: statins, essential phospholipids (EPL), and ursodeoxycholic acid (UDCA) (Table III).

Table II. Recommended diagnostic tests enabling the assessment of the severity of liver fibrosis

Recommended diagnostic tests to assess the severity of liver fibrosis	*N*	%
Non-invasive tests, e.g. FibroTest	149	11.3
Calculators, e.g. FIB-4, or NAFLD fibrosis score	76	5.7
FibroScan	275	20.8
Elastography	267	20.2
Other imaging studies: CT/MRI	664	50.2
Liver biopsy	296	22.4

Table III. Pharmacotherapy recommended to patients with NAFLD

Pharmacotherapy recommended to patients with NAFLD	*N*	%
Statins	614	46.4
Essential phospholipids (EPL)	645	48.8
Ursodeoxycholic acid (UDCA)	633	47.9
Vitamin E	342	25.9
ω-3 fatty acids	222	16.8
Thiazolidinediones	50	3.8
Others, e.g. milk thistle extract, L-ornithine L-aspartate, thiazolidine carboxylic acid	655	49.5
I do not recommend any drugs	121	9.2

Discussion

The results of our study show that NAFLD is the most common liver disease leading to medical consultations in Poland. In most cases, patients are less than 50 years old, in a smaller percentage between 51–70 years, and over three-quarters are patients with fatty liver.

In the Framingham Heart Study, in people with fatty liver (after the exclusion of people who abused alcohol – "heavy alcohol users") without known liver disease, higher mean serum levels of systemic markers of inflammation were found [10]. This would suggest that hepatic steatosis should be treated, and that reducing the inflammation might reduce the progression to NASH and subsequent stages of the disease and its complications. If treatment is not started, it is to be expected that in a dozen or so years the American prognosis [9] may also come true in other countries. The high prevalence of NAFLD in patients with type 2 diabetes underlines the need for early assessment of NAFLD in this group of patients [11].

A meta-analysis of 8,515,431 patients showed that obesity, dyslipidaemia (especially hypertriglyceridaemia), and diabetes were more frequently diagnosed in patients with NASH [1]. In a study of 432 patients with histologically confirmed NAFLD (26.8% NASH, 17.4% with moderate to severe fibrosis), diabetes and activity of aminotransferases proved to be independent prognostic factors of moderate to severe fibrosis and can be used to identify patients with NAFLD at risk of advanced fibrosis [12].

The results of our study indicated the important role of anamnesis, which often rules out toxic aetiology, including alcohol and other causes of chronic liver diseases.

It was also shown that the NAFLD diagnosis in the majority of cases was based on liver enzyme activity and abdominal ultrasound; non-invasive biochemical tests such as: SteatoTest, ActiTest, NashTest, or cytokeratin 18 were used less frequently, mainly by infectious disease specialists or diabetologists. This demands reflection, because the results of studies indicate that for the patients with NAFLD these tests are an alternative to liver biopsy [13].

In a survey study conducted among French gastroenterologists, non-invasive markers of fibrosis were used by 90% of respondents [14].

Liver biopsy is currently the most reliable test for NASH or liver fibrosis evaluation in patients with NAFLD, while aminotransferases activity, liver ultrasound, or other imaging tests such as computed tomography (CT) or magnetic resonance (MRI), do not accurately reflect the spectrum of histological changes in the liver [1]. In our study we found that liver biopsy was recommended in more than one fifth of NAFLD patients by infectious disease specialists and gastroenterologists to assess the severity of fibrosis.

A liver biopsy is not recommended as a screening test for NAFLD in a healthy population, nor is it recommended for asymptomatic patients with fatty liver in abdominal ultrasound examination, without significant risk factors for metabolic syndrome and insulin resistance. The indication for liver biopsy is a lack of biochemical improvement despite adherence to therapeutic recommendations, and abnormal results of non-invasive tests indicating liver fibrosis [15].

According to the current guidelines [1], the respondents recommended that their patients adopt a low-calorie low-fat diet, increase physical activity, and reduce body mass.

In our study, in addition to the change of lifestyle, specialists in outpatient clinics recommended statins and UDCA to almost half of the patients, while primary care physicians recommended that more than 50% of their patients use essential phospholipids (EPL), milk thistle extract, L-ornithine L-aspartate, and thiazolidine carboxylic acid. Pioglitazone was the most commonly prescribed drug among the drugs that increase insulin sensitivity.

NAFLD treatment is mainly based on the treatment of metabolic disorders, additionally supported by UDCA, the inclusion of which resulted in the reduction of liver enzymes. In a study by Ratziu *et al.* UDCA in a dose 28–35 mg/kg/day proved to be safe and well tolerated, and durably reduced the activity of alanine aminotransferase (ALT) as well as the severity of liver fibrosis, had a beneficial effect on glycaemic control, and improved insulin sensitivity [16].

In summary, it should be emphasised that patients with NAFLD visit doctors of various specialties, due to the wide spectrum of disorders accompanying this disease.

The limitation of this study is the inability to analyse data from medical records, instead using only the answers given by doctors.

The study revealed that many doctors prescribed pharmacotherapy not recommended in the treatment of NAFLD, which indicates the need to train doctors in the recommended treatment of this disease.

Conclusions

NAFLD was the most common liver disease that was the reason for medical consultations due to liver enzyme abnormalities and fatty liver in ultrasonography, but its incidence seems to be underestimated due to referral for further diagnosis only patients with abnormal aminotransferases.

The diagnostic methods used to assess the severity of liver fibrosis and the recommended pharmacological treatment varied depending on the doctors' specialisation and the type of medical centre (hospital or outpatient clinic) where they worked.

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Conflict of interest

The authors declare no conflict of interest.

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